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Ring-opening reactions of 2-aryl-3, 4-dihydropyrans with nucleophiles†

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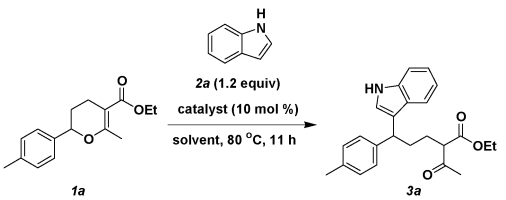
Ring-opening reactions of 2-aryl-3, 4-dihydropyrans with nucleophiles were reported for the first time. A possible mechanism was also proposed. Finally, this method was used in the synthesis of a novel tetrahydrocarbazole derivative that possesses a biologically active skeleton.

Dihydropyran and their derivatives are widely present in nature-occurring products.[1] Some of dihydropyrans showed important biological and pharmaceutical activities, and therefore, their synthesis has attracted much attention.[2] We have recently reported a three-component reaction of olefins, formaldehyde and *β*-dicarbonyl compounds, which generated a variety of 2,5,6-trisubstituted 3,4-dihydropyran derivatives in high yields (*see* electronic supporting information (**ESI**)†).[3] In view of the fact that this reaction opens, indeed, an easy access to the dihydropyrans, use of these products in organic synthesis becomes thus a downstream topic for us.

A literature survey stated that reactions of such substituted 3, 4-dihydropyrans have been rarely explored due perhaps to the difficulty of preparation.[4] Particularly, the 2-aryl-3, 4-dihydropyrans involve a benzyl ether fragment that is generally unstable in the presence of a nucleophile under acidic condition.[5] Therefore, we decided to evaluate the reactivity of these dihydropyrans towards nucleophiles with the aid of an acid catalyst. In this paper, we also describe a highly selective ring-opening reaction of 2-aryl-3, 4-dihydropyrans with nucleophiles, which offers a versatile method to link a *β*-dicarbonyl fragment together with the nucleophiles. To the best of our knowledge, only a few examples of ring-opening reactions of dihydropyrans have been performed so far,[6] and this type of ring-opening reaction has not been reported yet.

Indole has been frequently used as a nucleophile. In view of the great importance of indole derivatives in organic synthesis and pharmaceutical synthesis, we, thus investigated the reaction of a 2-aryl-3, 4-dihydropyran, **1a**, with indole, **2a** and the results are listed in Table 1. In the absence of catalyst, no reaction occurred (entry 1). When some weak acids, such as I_2 and boric acid, were used, a product, **3a**, was formed, but the yields obtained are rather poor (entries 2 to 3). Therefore, some commonly used strong acids, such as $Sc(OTf)_3$, $InCl_3$, $Bi(OTf)_3$ and TsOH were then examined in this reaction, and it was found that substrate **1a** was almost completely consumed, however, **3a** was obtained only in a small amount (entries 4 and 7). In these cases, many by-products that are difficult to isolate were observed by TLC detection. Solid acids, such as montmorillonite K10 and Amberlyst-15, were also used, and no significant improvement was observed (entries 8 and 9). Many other catalysts were also examined, and no good result was obtained (see **ESI**†). In order to improve the reaction yield, we then sought the help of a catalyst that has been rarely used in organic reactions, $MnCl_2{\cdot}4H_2O$. To our great delight, the model reaction proceeded smoothly in this case, and **3a** was finally obtained in 95% of yield (entry 10). Anhydrous $MnCl_2$ also worked well, but the yield of **3a** was inferior (entry 11). Further investigation revealed that the solvent also played a key role in controlling the catalytic activity of

Table 1 Ring-opening reaction of **1a** with **2a** in different conditions[a]



Entry	Catalyst	Solvent	Yield (%)
1	—	CH_3NO_2	0
2	I_2	CH_3NO_2	4
3	H_3BO_3	CH_3NO_2	5
4	$Bi(OTf)_3$	CH_3NO_2	12
5	$Sc(OTf)_3$	CH_3NO_2	31
6	$lnCl_3$	CH_3NO_2	20
7	TsOH	CH_3NO_2	28
8	Montmorillonite K10	CH_3NO_2	Trace
9	Amberlyst-15	CH_3NO_2	13
10	$MnCl_2{\cdot}4H_2O$	CH_3NO_2	95
11	$MnCl_2$	CH_3NO_2	52
12	$MnCl_2{\cdot}4H_2O$	Toluene	Trace
13	$MnCl_2{\cdot}4H_2O$	1,4-Dioxane	Trace
14	$MnCl_2{\cdot}4H_2O$	CH_3CN	31
15	$MnCl_2{\cdot}4H_2O$	DCE	39
16[b]	$MnCl_2{\cdot}4H_2O$	CH_3NO_2	93

[a] The reaction was performed in 0.25 mmol scale in 1.0 ml of solvent.
[b] The reaction was performed in 20 mmol scale.

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† Electronic supplementary information (ESI) available: Experimental details, Spectroscopic data of the products and ^1H and ^{13}C NMR profiles. See DOI: 10.1039/c1cc10355e

$MnCl_2·4H_2O$, and nitromethane proved to be an appropriate solvent for this system (entries 12 to 15).

With the optimized conditions in hand, we probed the scope of the reaction with respect to both the dihydropyrans and indoles. As shown in Fig. 1, a variety of dihydropyrans and indoles could be applied in the ring-opening reaction, and the corresponding products were obtained in good to excellent yields. Particularly, indoles substituted by a moderate electron-withdrawing group, such as 2-phenylindole, can also be used to react with a dihydropyran, **1b**, under catalysis of $MnCl_2·4H_2O$. A reaction in preparative-scale (20 mmol) was also investigated, and it was found that the reaction proceeded uneventfully, indicating the effectiveness of this method for practical synthesis (Table 1, entry 16). It should be noted that because the formed product contains not only a fragment of 1,3-dicarbonyl compound, but also an indole ring, it would not be unreasonable to expect that these products could be useful for organic synthesis. To the best of our knowledge, this is the first report for preparing this specific class of compounds.

The mechanism of the ring-opening reaction most likely involves a manganese-assisted nucleophilic substitution. Firstly, activation of the dihydropyran by a manganese(II) species is achieved *via* a cleavage of C–O bond in the ring. This is followed by nucleophilic attack of indole to the benzylcarbenium (**I**), which then leads to formation of the final product.[7] As a support of this mechanism, a dehydrogenation product of (**I**), **4a**, was also isolated in 22% by treating **1b** in the absence of nucleophile (Fig. 2). However, there was no product generated during the treatment of **4a** with indole. This result implies that (i) the benzylcarbenium (**I**) might be, indeed, formed, which can then generate both the desired product and **4a** depending on the reaction condition, and (ii) **4a** was not involved in the catalytic cycle. It is well known that organic reactions with a mechanism of an acid-catalyzed

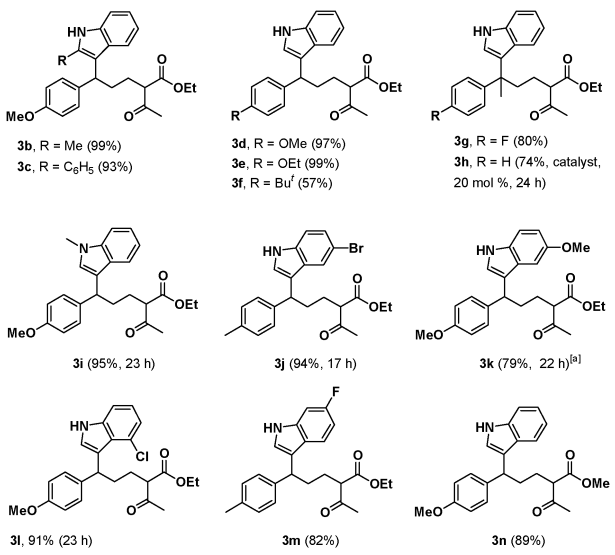


Fig. 1 Substrate scope of $MnCl_2·4H_2O$-catalyzed ring-opening reactions of 2-aryl-3, 4-dihydropyrans with thiophenols and thiols. Unless otherwise specified, all the reactions were conducted under the optimized condition in Table 1.

formation of benzylcarbenium are normally quite easy and insusceptible to the choice of acid catalyst.[8] However, in the model reaction, catalyst showed a significant effect on the performance. It might result from (i) the presence of keto-carbonyl that is also reactive toward the nucleophile under acidic conditions in the skeleton of the product; (ii) instability of the ester group under acidic condition, which tended to further convert the ring-opening product through a decarboxylation reaction pathway. Furthermore, when the electrophilic alkylation of the benzylcarbenium (**I**) to indole is unsuccessful, **4a**-type by-product might be generated as an alternative way to consume (**I**), which is also an acid-labile species. Realizing the ring-opening reaction, thus, is a challenge, and the key is how to control the catalysis driving toward the ring-opening product without disturbing the other coexistent organic functionalities. Kobayashi has accomplished a classification of many Lewis acids according to their activities in organic reactions.[9] In the ranking of Kobayashi, anhydrous $MnCl_2$ was considered as an inactive one. Therefore, we believe that acid strength of $MnCl_2$ might be responsible for the high selectivity. Furthermore, water might also play, to some extent, a role in tuning the Lewis acidity of $MnCl_2$ to be suitable for the reaction.

Other carbon-based nucleophiles, such as 2-naphthol and 4-hydroxy-6-methyl-2-pyrone, can also react with 2-aryl-3, 4-dihydropyrans in the presence of an appropriate catalyst (Scheme 1). These results imply that many other nucleophiles may also be applicable in this type ring-opening reaction, and the investigation is underway in our group.

High efficiency of these reactions led us to further explore their application in the synthesis of a complex molecule. It is known that 2-(3-arylpropyl)-β-diketones can undergo a radical cyclization to form a skeleton of tetrahydronaphthalene.[10] It occurred to us that cyclization of **3a**-type product might also be possible. Thus, we started a three-step synthesis involving: (i) a domino Knoevenagel/*oxo* Diels–Alder reaction of 4-methoxystyrene (**6a**), acetylacetone (**5a**) and aqueous formaldehyde that generated a dihydropyran **1c** in 93% of yield; (ii) $MnCl_2·4H_2O$-catalyzed ring-opening of **1c** with indole that generated the corresponding product, **3o**, in 91% of yield, and (iii) $Mn(OAc)_3$-promoted radical cyclization of **3o** in acetic acid. In the last step, both phenyl and indole rings are theoretically reactive toward the radical cyclization. Interestingly, only one product, **7a**, was obtained in 72% of yield, indicating that the indole ring is much more reactive than the phenyl ring under the present condition. It should be noted that skeleton of **7a** was known to possess biological activity.[11] Although method of accessing this skeleton is available, it only works for the synthesis of few molecules,[12] and how to modify the skeleton with substituent groups is still a challenge. The method in Scheme 2 not only offers an alterative way for the synthesis of this skeleton, but also is capable of modifying the structure in some specific positions, thus is valuable for organic synthesis.

In conclusion, ring-opening reactions of 2-aryl 3, 4-dihydropyrans with nucleophiles were described. Indoles, 2-naphthol and 4-hydroxy-6-methyl-2-pyrone could be used to react with an appropriate dihydropyran to form the corresponding ring-opening products. Skeletons of the obtained products contain

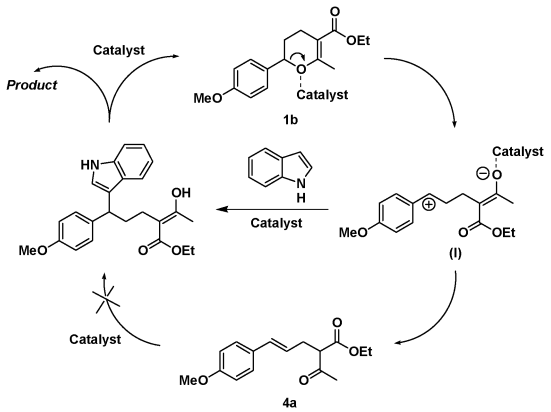
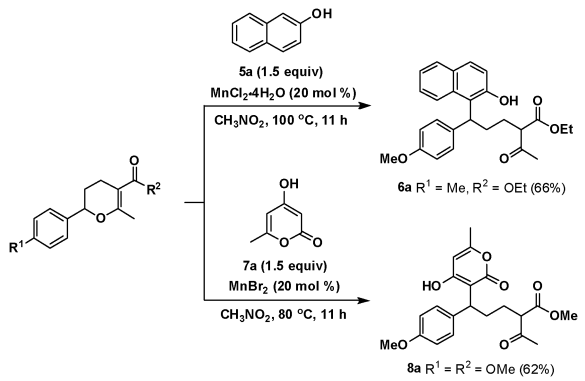
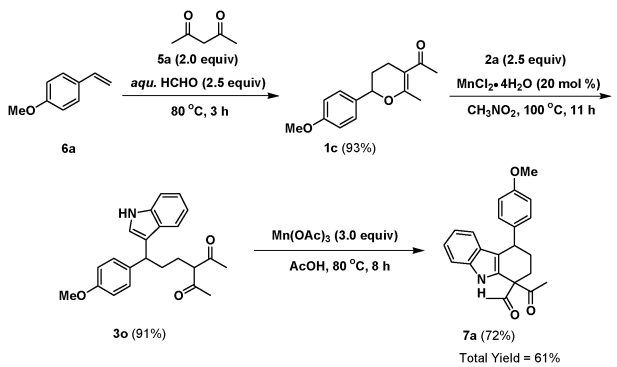


Fig. 2 Plausible mechanism of the ring-opening reaction of dihydropyran **1b** with a nucleophile.



Scheme 1 Ring-opening reaction of 2-aryl-3, 4-dihydropyran with other nucleophiles.



Scheme 2 Synthesis of 2, 3, 4, 9-tetrahydro-1*H*-carbazole **7a**.

not only a core structure of the nucleophile, but also a moiety of *β*-dicarbonyl compound. Particularly, because of the presence of 1,3-diketone moiety, the ring-opening product could be further cyclised through a radical pathway initiated by $Mn(OAc)_3$. Finally, a complex and valuable 2, 3, 4, 9-tetrahydro-1*H*-carbazole, **7a**, was prepared in an overall yield of 61% through a three-step synthesis starting from very simple substrates.

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